

## PHARMACEUTICAL FORMULATION

This invention relates to a solid, oral, controlled release pharmaceutical dosage form.

The literature is replete with examples of controlled release pharmaceutical preparations for oral usage.

PCT/SE93/00642 describes an oral morphine preparation having essentially complete bioavailability and, for the major part of the dissolution, an essentially zero order and essentially pH independent release of morphine for a period of at least 8 hours, in the form of a tablet having a core containing morphine sulphate and a buffering agent, the tablet core being coated with a diffusion membrane comprising a terpolymer of vinyl chloride, vinylacetate and vinylalcohol.

EP 0377518 describes a sustained release pellet composition containing a core element including at least one active ingredient of high solubility, and a core coating for the core element which is partly soluble at a highly acidic pH to provide a slow rate of release of active ingredient and wherein the active ingredient is available for absorption at a relatively constant faster rate in the intestines over an extended period of time such that blood levels are maintained within the therapeutic range over an extended period of time. A typical embodiment in this patent publication is a morphine sulphate containing preparation suitable for twice a day dosing obtained by a process which comprises coating core seeds with the active ingredient and then coating the resulting core seeds with a controlled release coating material containing ethyl cellulose, an acrylic co-polymer, a plasticiser and a detackifying agent using a solution of the aforesaid substances in an organic solvent.

PCT/SE94/00264 describes controlled release preparations containing a salt of morphine, comprising a number of core seeds coated with a barrier membrane. In the Example a conventional granulation is carried out with morphine hydrochloride, lactose and microcrystalline cellulose. The resulting morphine hydrochloride cores are then coated with a controlled release membrane containing hydroxypropyl methyl cellulose, ethyl cellulose and plasticisers using a solution of these substances in a mixed solvent of ethanol and methyl isobutyl ketone.

PCT/SE93/0025 describes a process for manufacturing sustained release pellets comprising pelletizing a mixture of a drug in finely divided form and a binder consisting of one or more water-insoluble wax-like binder substances with a melting point above 40°C, the pelletization being performed by mechanically working the mixture in a high shear mixer under the input of a sufficient amount of energy for the binder to melt and pelletization to take place. In a typical example in this patent publication paracetamol is pelletized using glycerol monostearate and optionally a lipophilic binder substance such as stearyl alcohol, triglyceride DS, Beeswax or microcrystalline wax, together with calcium hydrogen phosphate as a filler.

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EP 0636370 describes a sustained release pharmaceutical formulation containing morphine which is suitable for administration on a once daily basis. The dosage form is typically in the form of multiparticulates obtained by mechanically working in a high shear mixer a pharmaceutically acceptable morphine salt and a hydrophobic fusible carrier or diluent having a melting point from 35°C to 150°C and optionally a release control component comprising a water-soluble fusible material or a particulate, soluble or insoluble organic or inorganic material, at a speed and energy input which allows the carrier or diluent to melt or soften whereby it forms agglomerates, breaking down the agglomerates to give controlled release particles and optionally continuing mechanically working optionally with the addition of a low percentage of the carrier or diluent.

Embodiments are described in EP 0636370 in which the mean C<sub>max</sub> obtained in a group of five health volunteers when dosed at 60 mg of morphine sulphate is approximately 8 ng/ml and the W<sub>50</sub> value for morphine is approximately 8.6 hours.

The mean plasma curve includes a relatively high peak of about 10ng/ml at about 3 hours after dosing which tails off rapidly to reach a fairly stable, but declining level about 12 hours after dosing, with the ratio of mean C<sub>max</sub> to the mean plasma level at 24 hours of about 4.5.

According to the present invention there is provided a solid, oral, controlled release pharmaceutical dosage form which comprises a pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water at 25°C dispersed in a controlled release matrix, wherein the dosage form when tested by the Ph. Eur. Basket method at 100 rpm 900 ml aqueous buffer (pH 6.5) containing 0.05% w/w Polysorbate 80 at 37°C has an essentially zero order rate of release of the pharmaceutically active ingredient over a period of 8 hours, the amount of pharmaceutically active ingredient released over eight hours being in the range of 15% to 45% by weight, and when tested in a group of at least five healthy humans the median t<sub>max</sub>, based on blood sampling at half hourly intervals, is in the range of from 2.5 to 6 hours, and the ratio of mean C<sub>max</sub> to the mean plasma level at 24 hours is in the range of 1.5 to 3.5.

Polysorbate 80 is described in entry 7559 at page 1207 in Merck Index, Eleventh Edition 1989 published by Merck & Co. Inc. It is an oleate ester of sorbitol and its anhydrides copolymerised with approximately 200 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

A preferred dosage form in accordance with the invention has a median t<sub>max</sub> in the range from 2.5 to 3.5 hours.

In a preferred embodiment the dosage form according to the present invention has a mean W<sub>50</sub> in the range from 15 to 35 hours, more preferably 20 to 30 hours when tested in vivo as set forth above.

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In preferred embodiments the matrix comprises an hydrophobic, fusible material having a melting point of greater than 40°C and may also include a wicking agent which may be a hydrophilic, organic, polymeric, fusible substance or a particulate soluble or insoluble inorganic material.

In embodiments of the process of the invention described below it is believed the resulting matrix comprises an inner region which is a mixture comprising an hydrophobic, fusible material and active ingredient and preferably wicking agent surrounded by a contiguous, outer, mantle region comprising an hydrophobic, fusible material have a reduced concentration of, or being substantially free from, said pharmaceutically active ingredient and wicking agent, though the invention is not limited to this theory.

The pharmaceutically active ingredient is preferably present in an amount suitable for twice or once a day dosing. The preferred active ingredient is morphine or a pharmaceutically acceptable salt of morphine, preferably morphine sulphate or morphine hydrochloride and is preferably present in an amount suitable for once a day dosing. The dosage forms may preferably contain 30 to 400 mg of morphine as pharmaceutically acceptable salt.

The dosage form of the invention is conveniently in the form of a tablet or a capsule containing multiparticulates.

Although morphine and pharmaceutically acceptable morphine salts have been mentioned above as preferred active ingredients, other suitable water soluble active ingredients include hydromorphone hydrochloride, diamorphine hydrochloride tramadol hydrochloride and dihydrocodeine tartrate.

Preferably the weight ratio of hydrophobic, fusible material to wicking agent in the matrix or inner region thereof is in the range from 8:1 to 16:1 preferably 8:1 to 12:1.

Suitably the weight ratio of hydrophobic, fusible material in the said mixture to hydrophobic, fusible material in the mantle region is in the range of from 3:1 to 12:1.

Suitable hydrophobic, fusible materials are natural or synthetic waxes, oils, fatty acid glycerides or other esters for example hydrogenated vegetable oil or castor oil and suitable hydrophilic, organic, fusible wicking agents include polyethylene glycols (PEGs) of various molecular weights e.g. 1,000 to 20,000 preferably 4,000 to 10,000 and suitable particulate inorganic wicking agents include dicalcium phosphate and lactose. It is preferred to use an hydrophilic fusible, organic polymeric as wicking agent

The dosage forms of the present invention have a significantly lower C<sub>max</sub> and greater W<sub>50</sub> than dosage forms made according to the method described in EP 636370 whilst surprisingly retaining an advantageously short median t<sub>max</sub> of 2.5 to 6 hours.

Dosage forms of the present invention can be prepared by a process comprising:-

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- (a) mechanically working in a high shear mixer a mixture of hydrophobic, fusible binder and a minor amount of an organic, fusible, polymeric material which in the finished dosage form is capable of functioning as a wicking agent at a speed and temperature at which the binder melts or softens and the mixture forms agglomerates;
- (b) extruding the agglomerates whereby the extrudate is obtained as extruded pieces or an elongate extrudate is formed into pieces;
- (c) continuing mechanically working the pieces in a high shear mixer suitably until particles of reproducible in vitro release rate when tested according to the in vitro method set forth above have been achieved; and
- (d) continuing mechanically working with additional binder material at a temperature and speed at which the additional binder melts or softens and binds with the particles.

A preferred process uses identical hydrophobic, fusible material in stage (d) as in stage (a).

Preferably in stage (a) the weight ratio of hydrophobic, fusible material to wicking agent, preferably hydrophobic, organic, polymeric wicking agent, used is in the range from 8:1 to 16:1 preferably 8:1 to 12:1.

Preferably the weight ratio of hydrophobic, fusible material used in stage (a) to hydrophobic, fusible material use in stage (d) is in the range from 3:1 to 12:1 preferably 3:1 to 7:1.

The resulting multiparticulates may be sieved or otherwise size selected and filled into capsules e.g. hard gelatine capsules, or may be compressed into tablets. Usually the particles are of a size 0.5 mm to 3.0 mm and a spherical or spheroidal.

The higher shear mixer may be one conventionally used in the pharmaceutical formulation art and we have found satisfactory results can be achieved using a Collette Gral 75 or equivalent mixer.

Generally in stage (a) the mixture is processed until a bed temperature above 40°C is achieved and the mixture softens but does not melt and the resulting mixture acquires a cohesive granular texture, with particles ranges from 0.5 to 3.0 mm to fine powder in case of non-aggregated material. The mixture may be processed until it has the appearance of agglomerates which, upon cooling below 40°C have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance. The resulting mass is then extruded.

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Extrusion may be carried out by passing the agglomerates through a conventional extruder e.g. a Caleva extruder. An extruder may be used fitted with gears with suitably sized holes to provide pieces of desired size.

Usually the extrusion is through orifices having a diameter of about 0.25 mm to 1.5 mm eg 0.5 mm or 1.0 mm. The length of the extrudate pieces may be eg 0.5 to 1.5 cm eg 1.0 cm.

The preparation avoids the complicated forms of prior art preparations in that it does not require the use of controlled release coatings or buffers, whilst at the same time enabling dosing at only twice preferably once a day and without large fluctuations in blood plasma levels during the dosing intervals.

#### Example 1

The bowl of a Collette Gral 10 was preheated to a jacket temperature of 61°C and allowed to stabilise. 540.5g of morphine sulphate, 36g of polyethylene glycol 6000 and 343.2g of hydrogenated vegetable oil were placed in the pre-heated jacketed bowl and left to warm with no mixing for about 4 minutes.

The machine was then run for about 20 to 25 minutes with mixer and chopper blades running at 425 rpm and setting 1 respectively.

The resulting granules/agglomerates were then immediately removed and passed through a Caleva extruder fitted with 1mm hole gears.

The extruded pieces were placed in the bowl of the Collette Gral 10 which had been preheated to a jacket temperature of 61°C and left with no mixing for 4 minutes. Processing was then carried out as follows:-

- (a) for 4 minutes at mixer speed 100 rpm and chopper speed setting 1;
- (b) for 4 minutes at mixer speed 200 rpm, chopper setting 1 and jacket temperature 58°C; and
- (c) for 9 minutes at mixer speed 400 rpm, chopper setting 1 and jacket temperature 55°C.
- (d) 73g of hydrogenated vegetable oil were then added and processing was continued under the same conditions for a further minute.

The resulting multiparticulates were immediately passed through a sieve (0.5 to 2.0mm) and the 0.5-2.0mm fraction retained.

The retained multiparticulates were mixed with minor amounts of talc and magnesium stearate and encapsulated in hard gelatine capsules so that each capsule contained the following constituents.

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	mg
Morphine Sulphate BP	60.00
Hydrogenated vegetable oil NF	46.10
Polyethylene glycol 6000 Ph Eur	4.00
Talc Ph Eur	0.55
Magnesium Stearate Ph Eur	0.33

Example 2

Example 1 was repeated but using 526g of morphine sulphate, 35g of polyethylene glycol 6000, and 334g hydrogenated vegetable oil in the initial processing and subsequently adding 88g of hydrogenated vegetable oil in stage (d). Capsules were obtained containing multiparticulates having the following constituents:-

	mg/capsule
Morphine sulphate BP	60.00
Hydrogenated vegetable oil NF	48.10
Polyethylene glycol 600 Ph. Eur.	4.0
Talc Ph. Eur.	0.56
Magnesium stearate Ph. Eur	0.33

REFERENCE EXAMPLE 1

The multiparticulates obtained in Examples 1 and 2 were tested using the Ph. Eur Basket method at 100 rpm in 900 ml aqueous buffer (pH 6.5) containing 0.05% w/v Polysorbate 80 at 37°C and the release rates of morphine are shown in Table 1.

Hour	% Morphine released (mean)	
	Example 1	Example 2
1	4.7	2.7
2	8.6	5.4
3	12.6	8.1
4	16.3	11.0
5	20.4	13.8
6	24.3	16.8
8	32.2	22.9
10	39.7	29.3
14	53.4	41.1
24	76.6	62.7

REFERENCE EXAMPLE 2

The capsules obtained in Examples 1 and 2 and, by way of comparison, capsules obtained according to EP-A-636370 were tested in a single dose study in five healthy volunteers and blood samples were taken every half hour.

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The results are as shown in the following tables 2, 3 and 4.

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TABLE 2 - CAPSULE ACCORDING TO EP-A 636370 CONTAINING 60MG MORPHINE SULPHATE

Vol	Cmax (ng/ml)	tmax (h)	W50 (h)	C24 (ng/ml)	Cmax/C24
1	9.42	5	7.25	2.63	3.58
2	1.50	4	5.47	1.59	7.23
3	-	-	-	-	-
4	11.72	3	5.19	2.45	4.78
5	7.12	3	15.68	2.77	2.57
6	11.33	3	4.01	2.38	4.76
Mean	10.22		7.52	2.36	4.58
sd	1.96		4.71	0.46	1.74
Median		3			
Range		3-5			

TABLE 3 - CAPSULE ACCORDING TO EXAMPLE 1

Vol	Cmax (ng/ml)	tmax (H)	W50 (h)	C24 (ng/ml)	Cmax/C24
1	5.32	3	43.30	3.12	1.71
2	4.55	5	34.88	2.33	1.95
3	3.87	3	52.38	1.84	2.10
4	8.37	3	19.23	3.58	2.34
5	8.24	3	5.37	2.89	2.85
6	5.90	3	12.98	2.90	2.03
Mean	6.04		28.02	2.78	2.16
sd	1.88		18.39	0.61	0.39
Median		3			
Range		3-5			

TABLE 4 - CAPSULE ACCORDING TO EXAMPLE 2

Vol	Cmax (ng/ml)	tmax (H)	W50 (h)	C24 (ng/ml)	Cmax/C24
1	4.72	13	33.45	2.98	1.58
2	3.93	3	36.84	2.50	1.57
3	-	-	-	-	-
4	6.91	3	20.63	3.41	2.03
5	5.90	3	24.93	3.08	1.92
6	6.31	3	13.15	2.60	2.43
Mean	5.55		25.80	2.91	1.91
sd	1.21		9.59	0.37	0.36
Median		3			
Range		3-13			

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